Thanks Roger.
I noticed I had an extra copy of the Guidelines, which you can keep. I also have a copy of the SAB transcript. I know Mel Anderson very well. Mel was the Laboratory Director and I was the Toxicology Branch Chief. I assumed the Technical Director position in 1988 for the Govt tox Lab.
Robbie

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FORUM

Lessons Learned in Applying the U.S. EPA Proposed Cancer Guidelines to Specific Compounds

Melvin E. Andersen,* M. Elizabeth Meek,† Gary A. Boorman,‡ David J. Brusick,§ Samuel M. Cohen,¶ Yvonne P. Dragan,‖ Clay B. Frederick,‖‖ Jay I. Goodman,‖‖‖ Gordon C. Hard,# Ellen J. O'Flaherty,** and Denise E. Robinson††[1]

*Department of Environmental Health, Colorado State University; Fort Collins, Colorado; †Health Canada; ‡National Institute of Environmental Health Sciences; §Covance Laboratories; ¶University of Nebraska Medical Center; ‖Ohio State University; ‖‖Rohm and Haas Company; ‖‖‖Michigan State University; #American Health Foundation; **University of Cincinnati; and ††ILSI Health and Environmental Sciences Institute, Washington, DC

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An expert panel was convened to evaluate the U.S. Environmental Protection Agency's "Proposed Guidelines for Carcinogen Risk Assessment" through their application to data sets for chloroform ($CHCl_3$) and dichloroacetic acid (DCA). The panel also commented on perceived strengths and limitations encountered in applying the guidelines to these specific compounds. This latter aspect of the panel's activities is the focus of this perspective. The panel was very enthusiastic about the evolution of these proposed guidelines, which represent a major step forward from earlier EPA guidance on cancer-risk assessment. These new guidelines provide the latitude to consider diverse scientific data and allow considerable flexibility in dose-response assessments, depending on the chemical's mode of action. They serve as a very useful template for incorporating state-of-the-art science into carcinogen risk assessments. In addition, the new guidelines promote harmonization of methodologies for cancer- and noncancer-risk assessments. While new guidance on the qualitative decisions ensuing from the determination of mode of action is relatively straightforward, the description of the quantitative implementation of various risk-assessment options requires additional development. Specific areas needing clarification include: (1) the decision criteria for judging the adequacy of the weight of evidence for any particular mode of action; (2) the role of mode of action in guiding development of toxicokinetic, biologically based or case-specific models; (3) the manner in which mode of action and other technical considerations provide guidance on margin-of-exposure calculations; (4) the relative roles of the risk manager versus the risk assessor in evaluating the margin of exposure; and (5) the influence of mode of action in harmonizing cancer and noncancer risk assessment methodologies. These points are elaborated as recommendations for improvements to any revisions. In general, the incorporation of examples of quantitative assessments for specific chemicals would strengthen the guidelines. Clearly, any revisions should retain the emphasis present in these draft guidelines on flexibility in the use of scientific information with individual compounds, while simultaneously improving the description of the processes by which these mode-of-action data are organized and interpreted.

Key Words: chloroform; dichloroacetic acid; proposed cancer guidelines, U.S. EPA; mode of action; margin of exposure; harmonization; modeling, toxicokinetic; evidence, preponderance of; risk assessment.

In April 1996, the U.S. Environmental Protection Agency (EPA) published a set of "Proposed Guidelines for Carcinogen Risk Assessment" (U.S. EPA, 1996), the first revision since the original guidelines in 1986 (U.S. EPA, 1986). The proposed guidelines were developed as part of an interoffice program by a technical panel of the Risk Assessment Forum within EPA's Office of Research and Development. The proposed guidelines take into consideration the complexities of the carcinogenic process and the rapid pace of ongoing research in carcinogenesis. They acknowledge that insights gained from this research should be used to make more scientifically based assessments of the carcinogenic potential of chemical and physical agents with an emphasis on using mode-of-action information to project dose-response relationships. Although it is important that these guidelines remain general and flexible, it is anticipated that supplemental technical guidance documents will be developed when necessary. Following publication of the proposed guidelines in the Federal Register in April 1996, EPA requested public comments. The agency also expressed interest in developing chemical-specific case studies to illustrate and assess the strengths and limitations of the proposed guidance.

In September of 1996, an expert panel was convened by the

The opinions expressed herein are those of the Expert Panel members and do not necessarily reflect the views of their respective affiliations or the sponsoring organizations.

[1] To whom correspondence should be addressed at ILSI Health and Environmental Sciences Institute, 1126 Sixteenth Street, NW, Washington, DC 20036-4804. Fax: (202) 659-3617. E-mail: drobinson@ilsi.org.